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## VIRAL HEPATITISES OF MAN AND ANIMALS

[Following is the translation of an article by I. F. Barinskiy, Institute of Virology, AMN USSR, Moscow, published in the Russian-language periodical Voprosy Virusologii (Problems of Virology), No 3, 1967 pages 259-267. It was submitted on 13 Aug 1965.]

Viral hepatitises of man and animals are attracting all the more attention of investigators. This is explained by the fact that Botkin's epidemic hepatitis is a unique mass contagious disease of a viral nature which is wide-spread throughout the entire world and that the causative agent of it has not been isolated under laboratory conditions and has not been cultivated up until now by methods which are at the disposal of virologists. The importance of the problem is also conditioned by the irreparable damage to the health of man who carries epidemic hepatitis, often accompanied by transition of the infection into a chronic form and cirrhosis of the liver, and in cases of water outbreaks of the disease by a high mortality rate. It is also necessary to consider the tremendous harm to the economy which is inflicted by the yearly repeated mass outbreaks of the disease among man and animals.

The aspects of investigating viral hepatitises of man and animals are very diverse, but the key to the problem is the etiology of these diseases. The trend for a comparative study of viral hepatitises of man and animals, which has been developed since 1952 by A. K. Shubladze and associates, turned out to be a new and apparently promising approach to solving the problem of the etiology of viral hepatitises.

In this review we will present only certain data on the comparative study of viral hepatitises of man and animals.

In our country epidemic viral hepatitis in man is usually called Botkin's epidemic hepatitis, which stresses the priority of S. P. Botkin in the study of the infectious nature of this disease. This term encompasses both strictly hepatitis and serum hepatitis. In the latter infection takes place by infected preparations of blood during medical intervention. The international classification of diseases (European Symposium on Epidemic Hepatitis, Prague, 1964) distinguishes epidemic hepatitis from serum hepatitis. The latter disease is viewed as a complication following medical procedures. Such a breakdown is based mainly on epidemiological observations [24-26, 116], and also on the results of experiments on volunteers which made it possible to expose a number of peculiarities of serum hepatitis.

The ratio of morbidity rate between epidemic and serum hepatitis varies. Based on data from various investigators serum accounts for from 2-5 [96] up to 40% [33] of all the exposed cases of the disease. Recently some virologists [41] and also epidemiologists and clinicians [47, 91] are inclined to the opinion concerning the existence of a single causative agent of the disease.

Based on the data of some epidemiologists [38] the majority of people have had Botkin's epidemic hepatitis prior to 14 years of age. Therefore the main "fuel" for the infection are children and the peak of the rise in the morbidity rate occurs in the fall-winter months when they are gathered in organized collectives following summer vacations. It is characteristic that in animals the young usually come down with viral hepatitis. Such a pathology bears the names duckling hepatitis, piglet hepatitis, gosling hepatitis, etc. Anyone who has had anything to do with viral hepatitis in animals knows how difficult it is for an adult animal to become infected, therefore they prefer to work with newborn and very young animals. In outwardly healthy dogs which were not infected with hepatitis (for example, in 90% of the animals over 5 months old) antibodies to viral infectious hepatitis of dogs are contained in the blood sera [85]. This naturally developed immunity can be overcome only by a large dose of virus administered parenterally and by the influence of additional weakening factors: associated illness, exposure, and others. It is possible that such a situation develops in some adult persons following the parenteral administration of the virus with preparations of blood. The parenteral route of transmission of epidemic hepatitis was demonstrated already in 1945 [97].

The prolonged incubation period for serum hepatitis is explained [41] by the unusual way in which the virus penetrates into the organism (parenterally, under the protection of antibodies from the donor). This is also testified to by direct experiments on volunteers [59, 62] for clearing up the infectivity of the blood and separate fractions of it (including gamma-globulin) from patients with epidemic hepatitis. In these experiments an incubation period was revealed which was similar to that during serum hepatitis.

At present there is still no generally recognized strain or strains of virus of Botkin's epidemic hepatitis. All the data on the properties of the virus of epidemic hepatitis (or virus A according to the generally accepted classification) [27] and serum hepatitis (virus B) have been obtained only in experiments on volunteers. From the time of the first reports of such experiments, both in our country [40] and abroad [65], many similar investigations have been made [50, 66, 74, 94, 98, 99]; recent data of such a nature has been obtained in the experiments by Krugman and associates [82-84] and by Chapo [58-62]. In summarizing the results of the experiments on volunteers it is possible to be convinced of the great similarity between the viruses of epidemic and serum hepatitis. Thus it was shown that the virus of epidemic hepatitis is very resistant to the influence of physical and chemical factors.

The virus survives at 65° for 30 min, and it also survives ordinary chlorination of drinking water; it is inactivated by boiling for 10 min [73, 94, 105]. The highest degree of infectivity of materials from patients with epidemic hepatitis is revealed during the incubation period of the illness, especially during the second half of it [66]. Soon after the appearance of jaundice it fades away. The virus is revealed in the blood, feces, urine, duodenal secretion, and sometimes in discharges from the nasopharynx [66, 75, 95, 96]. In this respect there is interest in the data recently obtained by Giles, Liebhafner, and Krugman during experimental epidemic hepatitis (1964) [88]. In experiments on volunteers the virus was isolated from the blood on the 12th day of the incubation period, 25 days prior to the appearance of jaundice, and in the urine 5-6 days prior to the onset of jaundice. The virus was detected by contamination of a new consignment of volunteers, and also by the isolation of cytopathic agents.

Analogous data were obtained during the study of hepatitises of animals. In our investigations [42, 43] using the viruses of hepatitis of dogs, mice, and ducks, and also the viruses of yellow fever, Herpes, lymphocytic choriomeningitis, and ectromelia which caused a clearly expressed hepatitis in mice, it was also shown that the virus accumulates in the blood and liver of animals long before the first outward symptoms of the disease, in the period when the infected animals differed in no way from the control.

The virus of serum hepatitis B is also very resistant to the influence of physical and chemical factors. It survives in a frozen state (-20°) for several years, and in a dried state for at least a year. The virus is resistant to heating at 56° for 60 minutes [47]. It is well preserved in serum in which merthiolate in a concentration of 1:2000 or 0.2% tricresol has been added [193]. The size of the virus is around 30 mμ [102]. The virus is contained in a high concentration in the blood of patients during the incubation period of the disease long in advance (60 and even 87 days) of the appearance of jaundice [54]. The effectiveness of infection of volunteers with a very small amount of serum (0.01 ml) was demonstrated.

It is necessary to note that data on the extreme resistance of viruses of both epidemic and serum hepatitis to the influence of physical and chemical factors is not always substantiated. The investigations were conducted mainly with "icterogenic" sera. The results of recent investigations with agents isolated from patients with epidemic hepatitis showed that these viruses, just as all viruses, sharply increase their resistance when accommodated in serum [89]. Apparently the data obtained in experiments on volunteers concerning the unusual resistance of hepatitis viruses should be thoroughly checked under experimental conditions.

The above-cited results from a study of certain properties of the viruses of epidemic and serum hepatitis, which were obtained in experiments on volunteers, are convincing of their close similarity. In addition to this, as was already pointed out above [97], parenteral infection with the virus of epidemic hepatitis is possible. Therefore serum hepatitis can be viewed as a variant of epidemic. However, experiments conducted on volunteers for the purpose of isolating the virus of hepatitis B from the feces, urine, and discharges from the nasopharynx yielded negative results [74]. Besides this immunological differences between the viruses, which were revealed in experiments on volunteers, testified that persons who had had epidemic hepatitis are susceptible to serum hepatitis [40, 46].

The first circumstance can be explained by the small number of observations and by the fact that the volunteers used in the given experiment were persons who were resistant to infection. It is necessary to note that negative results were obtained following the infection of volunteers with sera from patients with serum hepatitis. The second circumstance can be explained, as this was demonstrated by us in experiments on animals, by the fact that during serum hepatitis large doses of virus were used in the form of icterogenic material which was administered parenterally. These overcame the immunity acquired during epidemic hepatitis. This problem requires further study.

It was also considered that gamma-globulin was effective in the prophylaxis of only epidemic and not serum hepatitis. However, recently (Geneva, 1965) it was demonstrated that in large doses (10 ml) this preparation prevents the development of infection with serum hepatitis also. This was confirmed in the recently conducted investigations by Dawson and Mirick [122, 123].

Since the time that the viral nature of epidemic viral hepatitis was established experiments have not ceased. These have the goal of isolating the virus from patients by means of infecting chick embryos and laboratory animals. The results of these tests showed that apparently at the present time man is the sole susceptible organism and also the sole source of infection. The question of whether or not monkey-primates can be a source of infection has still not been resolved [77, 121]. Attention is merited by the first positive tests on South American marmosets [128].

Numerous attempts to create a laboratory model of hepatitis on animals by using the method of provocation of infection (X-ray treatment [28], splenectomy [33, 34], and chemical provokers of liver function (ethionin for example)) were fruitless, and individual positive data [52, 53] need verification.

At present the tissue culture method is the only possible method for the isolation of viruses, the study of their properties, and the subsequent production of vaccine and diagnostic preparations.

With the help of this method it was possible to isolate a number of virus agents from materials taken from patients, including from the blood. The etiological role of these during viral hepatitis has still not been confirmed. Mainly tissue cultures of human origin were used: transplanted, primary trypsinized [3-6, 11], and finally diploid [88].

On the basis of various reports [115] in 1966 there are data concerning 18 virus groups isolated during hepatitis. Without dwelling on the properties of each of the strains isolated, we will note that only a few of them are related to now previously unknown viruses with original properties. Thus Chang [55] isolated a very fine (15 m $\mu$ ) virus, containing DNA and a large amount of lipids, which is manifested in a high degree of sensitivity of the virus to ether. In the sera of several convalescents antibodies were revealed in a large percentage of cases [56, 57].

From the blood of patients V. A. Ananyov and R. N. Abiyeva [1] isolated strains of adenovirus type 5 which caused hepatitis in sick suckling mice.

In hepatitis patients and donors Kachani [120] detected 144 strains of viruses which, according to his data, were devoid of a protein membrane and consisted of infectious DNA.

The majority of virus strains isolated during epidemic viral hepatitis did not differ from the known group of viruses. Many of them were related to the group of picornaviruses [122] and survive heating at 56° for 30 min and longer. However, there are no data confirming their etiological role in epidemic hepatitis. Reproduction of experiments for isolation of the same viruses have not been achieved by different investigators. Antibodies were revealed irregularly and in a small percentage of cases, their titers were low, and separate tests on volunteers [117] still did not yield sufficiently convincing results.

The reason for the diversity in the viruses isolated is still unknown. Each case of the isolation of the virus from a patient with a diagnosis of viral hepatitis requires a comprehensive consideration with the participation of epidemiologists, clinicians, and virologists. It is possible that during epidemic hepatitis damage to the reticulo-endothelial system of the organism and the hepatic parenchyma to a greater degree than during other infectious diseases conditions the disruption of the immunological reactivity of the organism. This may contribute to the penetration into the blood stream of certain so-called "normal residents" of the gastro-intestinal tract. The latter are revealed in the blood of patients by the very sensitive tissue culture methods which are in use at the present time. In addition to this many known viruses which cause specific clinical symptoms which are not connected directly with damage to the liver may sometimes (together with pathognomonic) cause pathological changes in the liver with the clinical manifestation of mildly expressed hepatitis.

It is also known that under certain conditions a number of well-studied viruses which cause diseases with a quite specific clinical picture may be the cause of severe hepatitises. Thus outbreaks or individual cases of illness among man have been described which were caused by adenoviruses [1, 31], the Herpes virus [95], Coxsackie B5 [114], type 2 rheovirus [44], Coxsackie A4 [96], and the virus of cytomegalia [32]. As a rule in each case the diagnosis of the disease was supported by the direct isolation of the virus from the blood of the patient or from the liver of a corpse and serologically. Severe damage to the liver during yellow fever [51], infectious mononucleosis [63, 79], and Rift valley fever [46] are also well-known. All of this serves as the reason for the advancement by some authors even of a hypothesis concerning the polyetiological nature of epidemic Botkin's hepatitis [45].

It is important to note, however, that in numerous experiments on volunteers [66, 74, 75, 92] and epidemiological investigations it has been shown that epidemic hepatitis is an individual nosological form of infectious disease which undoubtedly has its own specific causative agent. The complexity of studying this specificity under laboratory conditions is conditioned by the absence of strains of the original causative agent.

It has been demonstrated that a number of virus diseases of animals, for example adenovirus infection in birds [104], smallpox in mice [64, 109], sometimes are also accompanied by symptoms of severe hepatitis, and for lymphocytic choriomeningitis it was recently established [78] that there was a considerable concentration of virus in the liver of mice and it was reproduced in the cells of this organ during latent and acute infection.

Recently extensive use has been made of tissue culture methods for the isolation and study of animal hepatitis viruses. Only primary tissue cultures from the organs of young animals and embryos are used. It was particularly successful in isolating viruses with a clear cytopathic effect in kidney tissue [37, 71, 87, 115] and also in a tissue culture of macrophages [49]. It is interesting that kidney tissue from a human embryo was used successfully for the isolation of viruses from patients with epidemic hepatitis [3-5].

In summing up the data cited it can be noted that the very possibility of isolating viruses from the blood of patients with epidemic viral hepatitis stimulates virologists to conduct a constant search for the causative agent, and also to study and sort out the already isolated strains of the virus.

For proof of the etiological significance of the strains isolated during epidemic viral hepatitis it is necessary to compare the antigenic structure of the virus strains which were isolated by investigators in various regions and countries from the blood of patients with epidemic viral hepatitis and to subsequently study

and experiment with the most wide-spread strain. The carrying out of serological investigations with such a strain requires a statistically reliable amount of sera from patients and persons who have had the disease. Important data may be obtained in immunization experiments in foci of human infection with vaccines prepared from preliminarily selected inactivated strains of viruses.

Viral hepatitises of animals attract all the more attention of investigators. This group of diseases includes the viral hepatitises of dogs [7, 9, 108] and other animals of the canine family: polar foxes [35] and foxes [69, 75], and also mice [68, 100], ducklings [48, 107], goslings [118], canaries [89], rabbits [103], horses [29], piglings [79], and monkeys [77]. During the stated hepatitises damage to the liver is most often considered leading, if not the only symptom of disease of the organism.

The study of viral hepatitises of animals produced a whole series of new approaches to solving the question of the etiology of epidemic hepatitis. This implies the use of data concerning the infectivity of this or that material from sick animals and the periods in which this material was taken, the selection of sensitive tissue cultures, the method of processing the materials taken, ingredients of the nutrient medium for the tissue culture, etc. Besides this the study of viral hepatitises of animals makes it possible to answer those questions which may be resolved only on these models. These problems include first of all a study of the pathogenesis of viral hepatitises and the possibility of transplacental transmission of the infection and its after-effects on the organism of the mother and fetus, a study of morphological changes in a number of organs from patients during the dynamics of the infectious process, and the mechanism of latent and chronic infection during viral hepatitises.

In our experiments [12, 43] using the viruses of hepatitis of dogs and mice, and also using special equipment (aerosol chambers), it was shown in a various arrangement of experiments that the fecal-oral route of transmission of infection has primary significance in hepatitis of animals. The importance of feces and urine from sick animals in the dissemination of the virus is confirmed by the direct isolation of the virus of canine hepatitis [37] following trypsinization of animal kidneys. The virus, having penetrated through the wall of the gastro-intestinal tract, accumulates and reproduces in the mesenteric lymph nodes from where it penetrates into the blood. The role of the regional lymph nodes in the reproduction of the virus was demonstrated by us in experiments on the biological titration of the virus of hepatitis of mice, dogs, and ducks in different periods from the moment of contamination and by the method of immunofluorescence [13, 14], and also by Salenstedt [108, 110] for viral hepatitis of dogs by the method of fluorescent antibodies. Then the virus is spread with the flow of blood throughout the entire organism, damaging mainly



the reticulo-endothelial system. The virus accumulates and reproduces in organs which are rich in reticulo-endothelium: spleen, bone marrow, lymph nodes, including peripheral, the reticulo-endothelium of vessels, and, finally, the reticulo-endothelium of the liver. An important role in the spreading of the virus in the organism is apparently played by leukocytes and erythrocytes in the blood. This was confirmed by the detection, in the laboratory for comparative virology of the Institute of Virology imeni D. I. Ivanovskogo, of the phenomenon of erythrocytotropism of viruses in general and the virus of epidemic hepatitis in particular [19, 20, 86], and also by the cytogenetic change in the leukocytes in the patients' blood.

Thus in the light of the facts described viral hepatitises are more reticulotropic and hemotropic than hepatotropic infections. Damage to cells of liver parenchyma is observed only in the final phase of this disease with the incorporation of autoimmune processes [81, 111, 124, 125]. The sharply changed reticulo-endothelial and lymphoid systems of the organism are responsible for these. In this sense hepatitis and jaundice are not the onset of the disease, but an after-effect of it.

Confirmation of the above-cited virological data is the series of morphological investigations by B. K. Bezprozvanny, conducted jointly with V. A. Ananyev and I. F. Barinskiy [10, 14, 22] on a model of viral hepatitises of animals.

In the severity of clinical manifestations of the disease an important role is played by various secondary provocative factors [23], X-ray treatment in particular.

In experiments with viruses of mouse hepatitis [15] we, just as other authors, demonstrated the feasibility of the transplacental transmission of infection during many viral infections. This leads to the death of the fetus (up to 60%) and congenital malformations. The results of experimental investigations on models of viral hepatitis of mice confirm the clinical and epidemiological data of Stoller and Collmann [126, 127] concerning the role of the virus of Botkin's epidemic hepatitis in the etiology of the Dawn syndrome (mongolism) in newborn children.

The role of viruses from animal hepatitises in human pathology has not been cleared up to the end. The majority of authors consider that the hepatitis viruses are strictly adapted to "their" host. Data concerning the etiological role of viruses of animal hepatitis during human morbidity with hepatitis are founded mainly on the detection of antibodies to the virus of canine hepatitis in human sera [36, 90, 112], and in a paper which appeared recently - to the virus of mouse hepatitis. Data on the direct isolation of the virus from a human on a tissue culture of the lungs of a dog were presented only in one paper [113]. The results of our investigations on material from many hundreds of sera from patients with epidemic hepatitis [16-18] showed that antibodies to

the virus of infectious canine hepatitis are adenoviruses, anamnestic [?], and exposed in the sera of patients in the complement fixation reaction and the precipitation reaction in gel in view of the presence of a common antigen in adenoviruses and the virus of canine hepatitis. Similar antibodies were not revealed in the biological neutralization reaction in a tissue culture. Therefore in each specific case for confirmation of the etiological role of the viruses of hepatitis in man and animals it is necessary to have the isolation of the virus from the blood and feces of patients and the detection of an increase in antibody titer or the exposure of virus neutralizing antibodies in high titers.

Viral hepatitises of animals include a large group of viruses containing both RNA (hepatitis of mice and ducks for example) and DNA (canine hepatitis for example). Recently a great deal of attention is being given to adenoviruses of man and animals. This is explained not only by the fact that this group includes the virus of canine hepatitis but also by the direct isolation of adenoviruses in a large percentage of cases from the feces [30, 31] and also the blood of patients [2].

The cited data from contemporary investigations on the study of the etiology of hepatitises of man and animals testify to the new possibilities for the study of the isolated strains in tissue cultures and a comparative study of them by the method of animal infection.

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